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Article

Prevalence by therapy line and incidence of breast cancer brain metastases in 18 075 patients

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Abstract

Importance: Brain metastases portend poor prognosis in patients with metastatic breast cancer (MBC). Designing treatment and prevention clinical trials requires knowledge of brain metastases incidence with each line of therapy.

Objectives: We assessed the prevalence and cumulative incidence of brain metastases in a large MBC patient cohort by subtype and line of therapy, and the impact of HER2-low expression on prevalence.

Design, Setting and Outcomes: We analyzed brain metastases prevalence in patients with MBC in a nationwide electronic health record-derived de-identified database. The primary outcome was first diagnosis of brain metastases. We estimated prevalence and incidence of brain metastases by MBC subtype, including HER2-low and therapy line. We used the cumulative incidence function to estimate brain metastases risk in patients without brain metastases at initiation of systemic therapy. All *P*-values are 2-sided, and a *P*-value ≤.05 indicates statistical significance.

Results: Among 18 075 patients with MBC, 1102 (6.1%) had at least 1 brain metastasis at first-line therapy initiation. For the remaining 16 973 patients, cumulative incidence of brain metastases at 60 months was 10% in patients with hormone receptor-positive (HR+)/HER2− disease, 23% for HR+/HER2+ disease, 34% for HR−/HER2+ disease, and 22% for triple-negative breast cancer (TNBC). HER2-low expression within HR+/HER2− and TNBC subtypes had no impact on brain metastases incidence. Brain metastases prevalence increased per line of therapy for patients with all breast cancer subtypes.

Conclusions: Brain metastases incidence increases per line of therapy for every MBC subtype. The HER2-low biomarker does not impact brain metastases incidence within historical subtypes.

Introduction

The brain is a common site of metastasis for people with breast cancer, particularly for patients with the HER2-positive (HER2+) and triple-negative subtypes. Brain metastases are diagnosed in 30%-50% of patients with HER2+ and triple-negative metastatic breast cancer (MBC).[1-8] In contrast, brain metastases are less frequent (12%-15%) among patients with HR+/HER2− MBC.[4,5,7] A diagnosis of brain metastases usually portends poor overall survival and increased morbidity due to progressive neurologic deficits.[9] Thus, breast cancer brain metastases are an area of unmet medical need. Understanding the prevalence and cumulative incidence of brain metastases by line of therapy in a large, real-world dataset of patients with MBC may provide valuable insights into the impact of clinical trial exclusion criteria on enrollment of patients into therapeutic studies, develop a better understanding of the need for central nervous system (CNS)-active therapies by tumor subtype, and inform the design of studies to test the impact of CNS screening in patients with breast cancer.

Historically, patients with brain metastases have been excluded from large randomized trials of practice-changing HER2-targeted therapies such as trastuzumab, pertuzumab, and taxane chemotherapy and trastuzumab emtansine (T-DM1).[10,11] However, activity of T-DM1 in patients with brain metastases was suggested by the analysis of open-label studies or real-world evidence.[12,13] Recently, clinical trials of novel HER2-directed therapies, including new combination regimens and antibody-drug conjugates (ADCs), have included patients with brain metastases.[14-16] The HER2-directed ADC trastuzumab deruxtecan (T-DXd) has shown efficacy in patients with stable[17] and active brain metastases.[18] T-DXd has also shown excellent extracranial activity in patients with low levels of HER2 expression (termed HER2-low), leading to approval in this population.[19] HER2-low is

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a new therapeutic biomarker defined by immunohistochemistry (IHC) 1+ or 2+ with negative in situ hybridization (ISH). The impact of HER2-low expression on the incidence of brain metastases is unknown. However, early studies have shown preliminary evidence of intracranial efficacy of T-DXd in patients with HER2-low breast cancer brain metastases.[20] Given the improved intracranial activity of next-generation ADCs, understanding the incidence of HER2-low brain metastases is now relevant for the development of novel therapies for breast cancer brain metastases.

Brain metastases screening clinical trials are currently underway (NCT04030507). However, screening would be most relevant at the time in each patient's disease course when they are most likely to develop brain metastases. Yet, knowledge in this space is lacking. Understanding the incidence of brain metastases by line of therapy can help clinicians anticipate the likelihood of brain metastases at different stages of treatment. This information can guide treatment planning as well as the need for surveillance and preventive measures by subtype.

We conducted a longitudinal study using real-world data to learn about the prevalence per line of therapy and cumulative incidence of brain metastases in patients with MBC. We also assessed the association between HER2-low expression on the incidence of brain metastases per line of therapy.

Methods

Patient population

This study used the nationwide Flatiron Health electronic health record (EHR)-derived deidentified database and complied with the ethical standards of the Declaration of Helsinki.[21] The Flatiron Health database is a longitudinal database, comprising deidentified patient-level structured and unstructured data, curated via technology-enabled abstraction.[21,22] During the study period, the de-identified data originated from approximately 280 United States cancer clinics (approximately 800 sites of care). Eligible patients had initiated a first line of treatment (index date) for MBC up to March 1, 2021 to allow for at least 2 years of potential follow-up. Overall study design and patients' selection are detailed in Figure 1. Patients were categorized by hormone receptor (HR) and HER2 status as determined through abstraction. We incorporated a 28-day run-in period following the index date to allow for the comprehensive documentation of metastatic site workups and biomarker test results, thereby mitigating potential misclassification due to delayed entry. Overall, patients were classified as positive for a biomarker if at least 1 positive result was recorded up to the 28th day following the index date. Patients were classified as having HER2-low disease if they had HER2 IHC 1+ or IHC 2+ with no evidence of positive ISH results.[23] In a sensitivity analysis, HER2-low status was defined by the absence of IHC 3+ test results and an IHC 1+, IHC 2+, or equivocal result confirmed by a documented negative ISH test result. Site of metastases were retrieved from medical chart abstraction. Sites recorded up to the 28th day following index date were considered baseline characteristics. Lines of therapy were derived up to line 5 using treatment regimens and progression data. The deidentified data used in this study are subject to obligations to prevent reidentification and protect patient confidentiality.

Statistical analyses

The primary outcome was the first diagnosis of brain metastases. The prevalence proportion of brain metastases by subtype or line of therapy represents the fraction of patients who have a brain metastasis recorded up to the start of that line + 28 days, out of patients who were treated in that line. The cumulative incidence function of brain metastases was used to estimate the risk of brain metastases in patients free of brain metastases at the start date of the line of interest in the metastatic setting and death was treated as a competing event. Gray's test was used to compare the subdistribution hazard between lines of therapy.[24] All P-

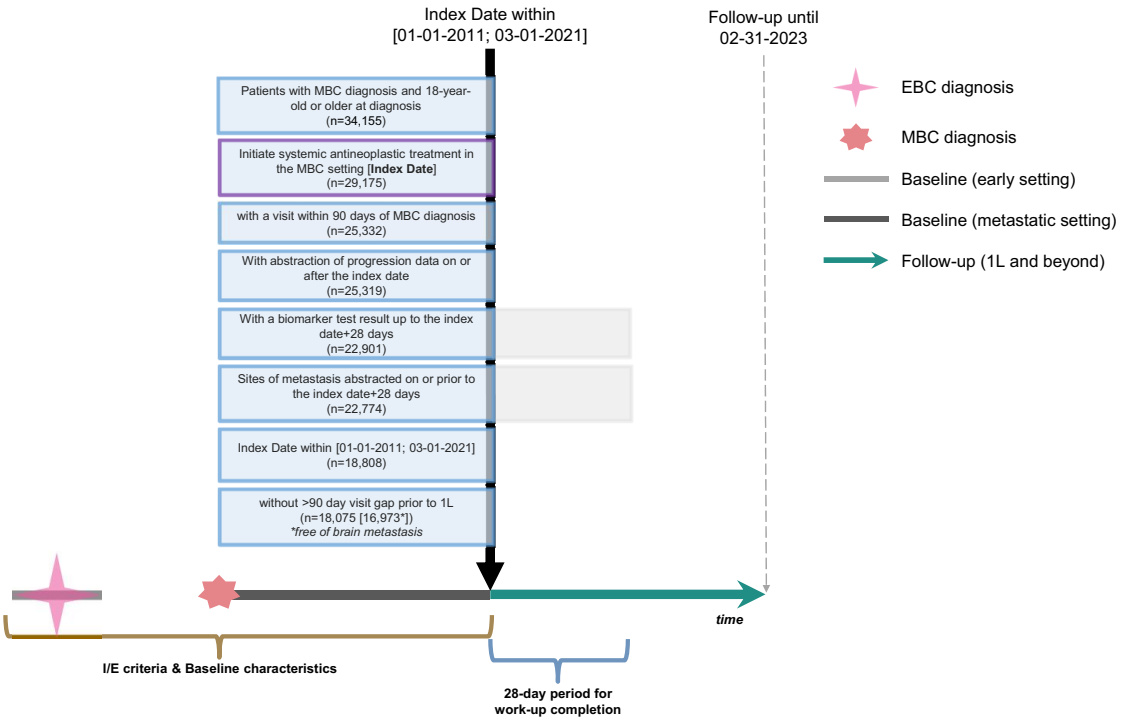

Figure 1. Study design and patients' selection. Abbreviations: EBC = early breast cancer; MBC = metastatic breast cancer.

values are 2-sided, and a *P*-value ≤.05 is the cutoff for statistical significance.

Results

Patient population

The study included data from 18 075 patients with MBC included in the real-world database (release date May 2023). Patient demographics and disease characteristics are reported in Table 1. Nearly one-third of patients (32.9%) were diagnosed with de novo MBC, and most patients (85.1%) received care at a community oncology practice. The majority of patients (68.2%) had HR+/HER2− breast cancer. Approximately 20% had HER2+ disease (HR+/HER2+: 16.9%; HR−/HER2+: 5.0%) and the remaining 9.8% had triple-negative breast cancer (TNBC).

Prevalence of brain metastases overall, by subtype and by line of therapy

At the time of initiation of the first line of systemic treatment, a total of 1102 patients (6.1%) had at least 1 brain metastasis, including 480 patients (3.9%) with HR+/HER2− disease, 280 (9.1%) with HR+/HER2+ disease, 118 (13.1%) with HR−/HER2+ disease, and 224 (12.6%) with TNBC.

The prevalence of brain metastases generally increased per line of therapy for patients with all breast cancer subtypes, including those with HER2-low disease (Table 2). However, the rate of increase differed by subtype. For patients with HR+/HER2− disease, the prevalence of brain metastases was 3.9% during the first line of therapy, and then rose steadily with each subsequent line, peaking at 10.7% by the fifth line of therapy. Although HR+/HER2− brain metastases have the lowest prevalence per subgroup, these cases represent that majority of brain metastases events due to the large proportion of patients with this subtype. For patients with HR+/HER2+ disease, the prevalence of brain metastases was 9.1% by first-line therapy and then rose to 22.9% by third line. For patients with HR−/HER2+ disease, the prevalence of brain metastases was 13.1% during the first line of therapy and rose sharply to 32.4% during the second line of therapy and remained close to 40% for all subsequent lines of therapy, suggesting that brain metastases are an early event for

Table 1. Clinical characteristics of cohort.

	No. of Patients (%)				
Characteristic (N = 18 075)	**Overall (N = 18 075)**	**HR+/HER2− (n = 12 331)**	**HR+/HER2+ (n = 3062)**	**HR−/HER2+ (n = 902)**	**TNBC (n = 1780)**
Median age, years (IQR)	64 (54-73)	65 (56-74)	61 (52-71)	60 (51-69)	61 (51-71)
MBC type					
De novo	5951 (32.9%)	3829 (31.1%)	1077 (35.2%)	463 (51.3%)	582 (32.7%)
Recurrent	12 090 (66.9%)	8478 (68.8%)	1979 (64.6%)	439 (48.7%)	1194 (67.1%)
NA	34 (0.2%)	24 (0.2%)	6 (0.2%)	0 (0%)	4 (0.2%)
ECOG PS					
0	5454 (30.2%)	3653 (29.6%)	956 (31.2%)	280 (31.0%)	565 (31.7%)
1	3728 (20.6%)	2480 (20.1%)	619 (20.2%)	184 (204%)	445 (25.0%)
2+	1683 (9.3%)	1174 (9.5%)	260 (8.5%)	81 (9.0%)	168 (9.4%)
Missing	7210 (39.9%)	5024 (40.7%)	1227 (40/1%)	357 (39.6%)	602 (33.8%)
Median number of metastases (IQR)	1 (1-2)	1 (1-2)	2 (1-3)	2 (1-3)	2 (1-3)
CNS metastases at index date					
Yes	1306 (7.2%)	620 (5.0%)	323 (10.5%)	124 (13.7%)	239 (13.4%)
No	16 769 (92.8%)	11 711 (95.0%)	2739 (89.5%)	778 (86.3%)	1541 (86.6%)
Brain Metastases at index date					
Yes	1102 (6.1%)	480 (3.9%)	280 (9.1%)	118 (13.1%)	224 (12.6%)
No	16 973 (93.9%)	11 851 (96.1%)	2782 (90.9%)	784 (86.9%)	1556 (87.4%)
Race/Ethnicity					
Hispanic/Latino	1337 (7.4%)	873 (7.1%)	239 (7.8%)	75 (8.3%)	150 (8.4%)
Non-Hispanic Asian	381 (2.1%)	244 92.0%)	78 (2.5%)	20 (2.2%0	39 (2.2%)
Non-Hispanic Black	2072 (11.5%)	1215 (9.9%)	365 (11.9%)	119 (13.2%)	373 (21.0%)
Non-Hispanic Other	1522 (8.4%)	1016 (8.2%)	277 (9.0%)	93 (10.3%)	136 (7.6%)
Non-Hispanic White	11 459 (63.4%)	8101 (65.7%)	1893 (61.8%)	517 (57.3%)	948 (53.3%)
Unknown	1304 (7.2%)	882 (7.2%)	210 (6.9%)	78 (8.6%)	134 (7.5%)
Region					
Midwest	2354 (13.0%)	1679 (13.6%)	362 (11.8%)	98 (10.9%)	215 (12.1%)
Northeast	2727 (15.1%)	1964 (15.9%)	405 (13.2%)	127 (14.1%)	231 (13.0%)
South	6597 (36.5%)	4346 (35.2%)	1166 (38.1%)	356 (39.5%)	729 (41.0%)
Unknown	3639 (20.1%)	2463 (20.0%)	602 (19.7%)	183 (20.3%)	391 (22.0%)
West	2758 (15.3%)	1879 (15.2%)	527 (17.2%)	138 (15.3%)	214 (12.0%)
Practice type					
Community	15 385 (85.1%)	10 499 (85.1%)	2608 (85.2%)	767 (85.0%)	1511 (84.9%)
Academic	2424 (13.4%)	1653 (13.4%)	413 (13.5%)	123 (13.6%)	235 (13.2%)
Both	266 (1.5%)	179 (1.5%)	41 (1.3%)	12 (1.3%)	34 (1.9%)
Payer category					
Commercial health plan	9828 (54.4%)	6657 (54.0%)	1700 (55.5%)	477 (52.9%)	994 (55.8%)
Medicaid	550 (3.0%)	336 (2.7%)	98 (3.2%)	49 (5.4%)	67 (3.8%)
Medicare	2101 (11.6%)	1552 (12.6%)	306 (10.0%)	74 (8.25%)	169 (9.5%)
Other	1167 (6.5%)	755 (6.1%)	213 (7.0%)	74 (8.2%)	125 (7.0%)
NA	4429 (24.5%)	3031 (24.6%)	745 (24.3%)	228 (25.3%)	425 (23.9%)
Median visit rate (IQR)	0.10 (0.06-0.17)	0.10 (0.06-0.17)	0.10 (0.06-0.17)	0.11 (0.07-0.16)	0.11 (0.07-0.18)

Abbreviations: CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; MBC = metastatic breast cancer; TNBC = triple-negative breast cancer.

this subtype. Among patients with TNBC, the prevalence of brain metastases was 12.6% during the first line of therapy and rose steadily with each line, peaking at 30.5% during the fifth-plus line of therapy.

Incidence of brain metastases overall, by subtype and by line of therapy

Overall, amongst the 16 973 patients free of brain metastases at the first-line therapy, 2248 (13.2%) had an incident brain metastasis event during follow-up, 9314 had a competing event, and 5411 were censored. The cumulative incidence of brain metastases at 60 months was 10% in patients with HR+/HER2− disease, 23% for patients with HR+/HER2+ disease, 34% in patients with HR−/HER2+ disease, and 22% in patients with TNBC (Figure 2 and Table 3).

The cumulative incidence of brain metastasis at 60 months increased from 10.2% to 14% for the patients with the HR+/HER- subtype initiating their first and fifth line, respectively. Conversely, other subtypes exhibited a decrease from 22.7% to 12.4%, 33.6% to 25%, and 22.3% to 18.4% for the HR+/HER2+, HR−/HER2+ and TNBC subtype, respectively (Table 3 and Figure S1).

Association between HER2-low status on brain metastases incidence

When evaluated over time and by HER2 IHC status, the incidence of brain metastases was higher among patients with HER2 IHC 3+ or 2+ ISH/amplified than among those with HER2-low or HER2 IHC 0 breast cancer (Figure S2). At 12 months, the incidence of brain metastases was 9.94% among patients with HER2 IHC 3+, 6.59% among those with HER2 IHC 2+/ISH+, 3.84% among those with HER2-low, and 5.45% among those with HER2 IHC 0 breast cancer. At 60 months, the incidence of brain metastases was 28.4% among patients with HER2 IHC 3+, 17.3% among those with HER2 IHC 2+/ISH+, 11.0% among those with HER2-low, and 12.8% among those with HER2 IHC 0 disease.

The prevalence of brain metastases by line of therapy was assessed among patients with HER2-low disease separately within the HR+/HER2-negative and triple-negative subtypes. The prevalence and incidence of brain metastases was nearly identical throughout all lines of therapy for all patients with the HR+/HER2-negative and TNBC subtypes and patients with HER2-low breast cancer within each subtype, respectively (Table 2). The sensitivity analysis resulted in similar findings. The vast majority of HER2-low patients are HR+/HER2−. By fifth line therapy, 9.7% of HR+/HER2− and 10.5% of HR+/HER2-low patients had brain metastases (Figure S3). The cumulative incidence functions were also very similar between HER2-low and historical subtypes (Figure S4).

Incidence of brain metastases by race/ethnicity

Among all patients, the cumulative incidence of brain metastases was lower among Non-Hispanic White patients than those of all other races and ethnicities (Figure S5, A). When analyzed by subtype, there was no association between race/ethnicity and cumulative incidence of brain metastases among patients with HR+/HER2− (Figure S5B), HR+/HER2+ (Figure S5C), or HR−/HER2+ breast cancer (Figure S5D). Among patients with TNBC, there was a trend toward higher cumulative incidence of brain metastases among Non-Hispanic Asian patients, but this association was not statistically significant (Figure S5, E).

Discussion

Brain metastases are a common and often devastating event for MBC patients. Several prior studies have evaluated the incidence of brain metastases over time and by subtype in patients with MBC, both recurrent and de novo. Wang et al.[7] conducted a population-based cohort study of 3916 patients with de novo MBC whose information was available in population health administrative databases in Ontario, Canada. Notably, CNS metastases were not directly captured in the databases. Thus, the authors used the initiation of brain radiation therapy as a proxy for the diagnosis of brain metastases. Using these criteria, the cumulative incidence of brain metastases was 12.1% for patients with HR+/HER2− breast cancer, 28.1% for those with HR+/HER2+ disease, 34.7% for those with HR−/HER2+ disease, and 21.9% for those with TNBC. Although there was a general increase in brain metastases over time in all patients, the rate of increase varied by subtype. For example, the cumulative incidence of brain metastases among patients with HR+/HER2− breast cancer was 3.8% at 1 year and 8.2% at 3 years after diagnosis. The corresponding 1- and 3-year cumulative incidences were 5.2% and 17.7% for HR+HER2+, 11.0% and 25.3% for HR−/HER2+, and 12.9% and 21.4% for TNBC. In line with our findings, these results demonstrate that brain metastases are more common among patients with HER2+ and TNBC, and are often an early event in these subtypes.

Darlix et al.[25] evaluated the prevalence of CNS metastases among 16 701 MBC patients included in the French *Epidemiological Strategy and Medical Economics* (ESME) research program, which includes 18 participating French specialized cancer centers. Among these patients, 4800 had de novo MBC and 11 901 had

Table 2. Prevalence of brain metastases per subtype (including HER2-low) and line of therapy.

Line of Therapy	HR+/HER2− [HR+/HER2-low]	HR+/HER2+	HR−/HER2+	TNBC [HR−/HER2−low]
No. of patients				
1	12 331 [7062]	3062	902	1780 [752]
2	8120 [4721]	1936	478	972 [422]
3	5303 [3101]	1232	281	526 [240]
4	3454 [2002]	761	159	283 [129]
5	2191 [1276]	453	103	141 [70]
Prevalence of brain metastases (%)				
1	480 (3.9%) [293 (4.1%)]	280 (9.1%)	118 (13.1%)	224 (12.6%) [99 (13.7%)]
2	470 (5.2%) [303 (6.4%)]	361 (18.6%)	155 (32.4%)	179 (17.5%) [77 (18.2%)]
3	395 (7.4%) [258 [8.3%)]	282 (22.9%)	109 (38.8%)	121 (23.0%) [53 (22.1%)]
4	318 (9.2%) [202 (10.1%)]	210 (27.6%)	61 (38.4%)	75 (26.5%) [37 (28.7%)]
5	235 (10.7%) [144 (11.3%)]	124 (27.4%)	39 (37.9%)	43 (30.5%) [18 (25.7%)]

Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple-negative breast cancer.

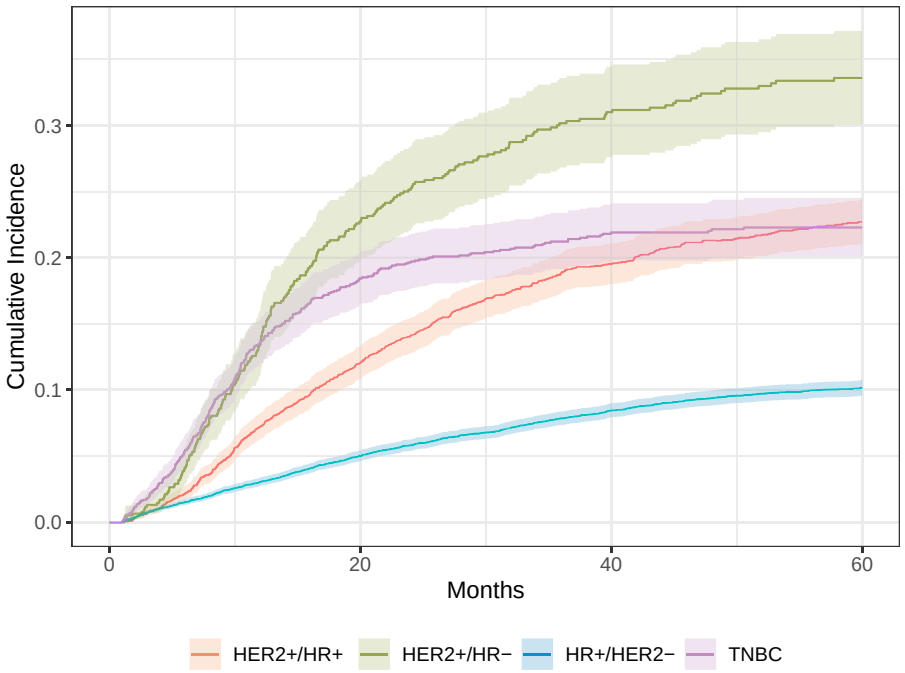

Figure 2. Cumulative incidence of brain metastases up to 60 months. Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple-negative breast cancer.

Table 3. Cumulative incidence of brain metastases up to 60 months per subtype and line of therapy.

Subtype and line	No.[a]	No. Event[b]	Month 12	Month 24	Month 36	Month 60	P[c]
HR+HER2−							<.001
1Line	11 851	1119	3.1% (2.8%, 3.4%)	5.8% (5.4%, 6.3%)	7.9% (7.4%, 8.4%)	10.2% (9.6%, 10.8%)	
2Line	7650	798	4.6% (4.1%, 5.1%)	7.8% (7.2%, 8.5%)	10.1% (9.4%, 10.8%)	12.2% (11.4%, 13.0%)	
3Line	4908	551	5.7% (5.1%, 6.4%)	9.8% (8.9%, 10.7%)	12.0% (11.0%, 13.0%)	13.4% (12.3%, 14.5%)	
4Line	3136	369	6.9% (6.0%, 7.8%)	11.3% (10.2%, 12.6%)	12.8% (11.6%, 14.1%)	14.2% (12.9%, 15.7%)	
5Line	1956	225	7.8% (6.6%, 9.1%)	11.6% (10.1%, 13.1%)	13.0% (11.4%, 14.6%)	14.0% (12.3%, 15.8%)	
HR+HER2+							<.001
1Line	2782	578	7.2% (6.3%, 8.3%)	14.1% (12.8%, 15.5%)	18.8% (17.3%, 20.4%)	22.7% (21.0%, 24.4%)	
2Line	1575	270	8.7% (7.4%, 10.2%)	14.5% (12.7%, 16.3%)	17.5% (15.5%, 19.6%)	20.3% (18.1%, 22.6%)	
3Line	950	140	8.7% (7.0%, 10.7%)	13.7% (11.4%, 16.1%)	16.6% (14.1%, 19.3%)	18.0% (15.3%, 20.9%)	
4Line	551	68	7.2% (5.1%, 9.6%)	12.0% (9.2%, 15.1%)	14.6% (11.5%, 18.0%)	15.4% (12.1%, 19.1%)	
5Line	329	33	5.7% (3.4%, 8.7%)	10.0% (6.8%, 13.9%)	12.4% (8.7%, 16.7%)	12.4% (8.7%, 16.7%)	
HR-HER2+							.041
1Line	784	237	13.4% (11.1%, 16.0%)	25.1% (22.0%, 28.4%)	30.2% (26.8%, 33.6%)	33.6% (30.1%, 37.1%)	
2Line	323	75	14.5% (10.9%, 18.7%)	19.6% (15.3%, 24.3%)	24.1% (19.3%, 29.3%)	26.7% (21.5%, 32.1%)	
3Line	172	33	11.2% (6.9%, 16.7%)	19.6% (13.7%, 26.3%)	21.3% (15.1%, 28.2%)	23.0% (16.1%, 30.7%)	
4Line	98	18	11.7% (6.2%, 19.1%)	18.9% (11.5%, 27.7%)	18.9% (11.5%, 27.7%)	22.5% (12.9%, 33.7%)	
5Line	64	13	16.5% (8.4%, 27.0%)	20.1% (10.9%, 31.1%)	20.1% (10.9%, 31.1%)	25.0% (12.5%, 39.7%)	
TNBC							.7
1Line	1556	314	13.5% (11.8%, 15.3%)	19.6% (17.6%, 21.7%)	21.2% (19.1%, 23.4%)	22.3% (20.1%, 24.5%)	
2Line	793	157	14.7% (12.3%, 17.3%)	19.7% (16.9%, 22.7%)	21.3% (18.4%, 24.4%)	21.8% (18.8%, 24.9%)	
3Line	405	70	13.2% (10.0%, 16.8%)	17.9% (14.1%, 22.0%)	19.0% (15.1%, 23.2%)	19.6% (15.5%, 24.0%)	
4Line	208	31	12.1% (7.9%, 17.2%)	15.3% (10.5%, 21.0%)	18.0% (12.5%, 24.3%)	18.0% (12.5%, 24.3%)	
5Line	98	15	12.7% (6.7%, 20.7%)	18.4% (10.7%, 27.7%)	18.4% (10.7%, 27.7%)	18.4% (10.7%, 27.7%)	

[a] Number of patients free of brain metastasis at the initiation of the line of therapy.
[b] Number of brain metastasis event observed during the totality of follow-up available.
[c] Gray's Test.
Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple-negative breast cancer.

recurrent MBC. After a median follow-up of 42.8 months, 24.6% of patients developed CNS metastases. At 12 and 24 months of follow-up, the cumulative incidence of CNS metastases per subtype was 8.3% and 14.4% for HR+/HER2−, 16.8% and 29.2% for HR+/HER2+, 32.4% and 49.0% for HR−/HER2+, and 29.8% and 44.8% for TNBC. The incidence continued increasing over time for all subtypes, for a final cumulative incidence of 36.9% for HR+/HER2−, 53.5% for HR+/HER2+, 72.6% for HR−/HER2+, and 71.3% for TNBC.

Aversa et al. conducted a retrospective study of 488 MBC patients treated at a single outpatient clinic in Italy. Among these patients, 115 (24%) developed CNS metastases. The cumulative incidence per subtype was 14% for HR+/HER2−, 35% for HR+/HER2+, 49% for HR−/HER2+, and 22% for TNBC.[4]

Our present study differs from others in that we documented the prevalence of brain metastases by subtype and by line of therapy as well as the cumulative incidence of brain metastases among 16 973 MBC patients who were free of brain metastases at the time of first-line therapy initiation. Consistent with prior studies,[4,25] the prevalence of brain metastases was highest among patients with HR−/HER2+ breast cancer and TNBC and lowest among those with HR+/HER2− disease. This adds to the body of literature as our dataset is a clean evaluation of the incidence of brain metastases by line of therapy and by subtype in breast cancer patients free of brain metastases at baseline. This information will be useful for clinical trial planning purposes, screening risk assessment, and patient counseling. For patients with all breast cancer subtypes, the prevalence of brain metastases generally increased over time and with each line of therapy. However, the rate of increase differed by subtype. Patients with HR+/HER2− breast cancer had a roughly linear increase in the prevalence of brain metastases over time and with each line of therapy. For patients with HR−/HER2+ breast cancer, the prevalence of brain metastases doubled between 12 and 24 months (13%-25%) and nearly tripled between the first and second line of therapy (11.2%-31.2%). In line with prior work,[7] these findings further demonstrate that brain metastases are frequent in patients with HR−/HER2+ MBC and often occur early in the development of the disease. Moreover, these findings emphasize the importance of ongoing screening clinical trials (particularly at critical time points such as transitions between treatment lines) and have significant clinical implications for the design of screening and prevention trials. Tailored surveillance strategies are warranted to identify high-risk patient subgroups and prioritize resource allocation. These data also highlight the need to include patients with a history of brain metastases in clinical trials and the dramatic number of real-world patients that would be invisible and unrepresented in clinical trials with brain metastases exclusion.

We also describe the impact of HER2-low expression on the prevalence of brain metastases in patients with HER2-negative breast cancer. HER2 overexpression is a major risk factor for the development of brain metastases[1-8]; however, the impact of HER2-low expression is less well studied. Among all patients, the cumulative incidence of brain metastases was higher for patients with HER2 IHC 3+ compared with HER2-low or HER2 IHC 0 disease. Among patients with HR+/HER2− and TNBC, HER2-low status appeared to have no impact on the prevalence of brain metastases at any time in our analysis. This finding was very recently also found in a large database series of 4727 with breast cancer brain metastases.[26] This finding suggests that factors other than lower-level HER2 expression may primarily drive the risk of brain metastases in these breast cancer subtypes. Yet, the HER2-low status was observed in an appreciable number of HR+/HER2− and TNBC patients with brain metastases offering opportunities to further develop antibody drug conjugates with intracranial efficacy such as trastuzumab deruxtecan in these populations. Overall, these findings contribute to a better understanding of the molecular determinants of brain metastases and can inform personalized treatment strategies for patients with HR+/HER2− breast cancer and TNBC.

Preventing the development of brain metastases is a worthwhile endeavor, but it will not help the subset of breast cancer patients with synchronous brain metastases. In the present study, 1102/18 075 patients (6.1%) had at least 1 brain metastasis at the date of diagnosis of metastatic disease, which generally agrees with prior population-based studies.[27,28] In a previous population-based study using data from the Survival, Epidemiology, and End Results (SEER) database, 968 of 238 726 adult breast cancer patients (0.41%) had brain metastases at the time of breast cancer diagnosis. Notably, this comprised 7.56% of all patients with metastatic disease to any site at the time of breast cancer diagnosis (n = 12 801). The prevalence was highest among patients with HR−/HER2+ disease (0.7% of the overall cohort; 11.4% of patients with metastatic disease at diagnosis).[27] Another population-based study also using SEER data included 568 920 patients diagnosed with breast cancer between 2010 and 2018, including 30 960 with de novo MBC. Among all patients in the study, 2248 had brain metastases at diagnosis, which accounted for 0.40% of all patients and 7.26% of patients with metastatic disease.[28]

These data also inform optimal approaches to the design of breast cancer prevention clinical trials. To date, primary prevention of brain metastases has not been achieved. The goal of primary prevention is to prevent brain metastases from occurring in patients with advanced cancer or high risk of developing advanced cancer. This study provides a relevant historical reference for incidence by subtype and per line of therapy for powering clinical trials adequately. This work also suggests that primary prevention trials would need to occur in early lines of therapy for HR−/HER2+ as more than one-third will develop brain metastases by third line therapy. Prevention trials in HR+/HER2+ or HR+/HER2− breast cancer would be more challenging because brain metastases seem to be more slowly distributed over time so that prevention approaches would need to have a long time frame of impact to have an effect.

The findings from this study offer valuable insights into when CNS active therapies are needed relative to line of therapy by tumor subtype. By third line therapy, more than 22.9% of HR+/HER2+, 38.8% of HR−/HER2+, and 23.0% of TNBC patients will have developed brain metastases. Excluding patients with history of brain metastases in these subgroups would make attribution of novel therapeutic efficacy to real-world populations impossible. By third line therapy, many patients in these subgroups are at risk of brain metastases and systemic therapies would ideally have CNS penetrant properties.

These findings also present optimal timing for screening and prevention of breast cancer brain metastases. Moving forward, research should focus on identifying molecular drivers of brain metastases, identifying predictive biomarkers of brain metastasis development, and developing targeted preventive strategies. Clinical trials of early screening protocols and tailored surveillance strategies are underway. These include the randomized phase III CompassHER2 RD (Alliance A011801) trial of postneoadjuvant T-DM1 with either tucatinib or placebo in patients with high-risk early-stage HER2+ breast cancer with residual invasive disease after neoadjuvant therapy. The primary endpoint is iDFS, and brain metastases-free survival is a key secondary endpoint, under the hypothesis that the combination of T-DM1 and tucatinib will be more effective than T-DM1 and placebo at preventing CNS relapse.[29]

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Author contributions

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Supplementary material

Supplementary material is available at *JNCI: Journal of the National Cancer Institute* online.

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Conflicts of interest

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Data availability

The data that support the findings of this study have been originated by Flatiron Health, Inc. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to: dataaccess@flatiron.com

References

1. Hurvitz SA, O'Shaughnessy J, Mason G, et al. Central nervous system metastasis in patients with HER2-positive metastatic breast cancer: patient characteristics, treatment, and survival from SystHERs. *Clin Cancer Res*. 2019;25:2433-2441.
2. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer*. 2003;97:2972-2977.
3. Lai R, Dang CT, Malkin MG, et al. The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma. *Cancer*. 2004;101:810-816.
4. Aversa C, Rossi V, Geuna E, et al. Metastatic breast cancer subtypes and central nervous system metastases. *Breast*. 2014;23:623-628.
5. Kuksis M, Gao Y, Tran W, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. *Neuro Oncol*. 2021;23:894-904.
6. Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). *Lancet Oncol*. 2013;14:244-248.
7. Wang XY, Rosen MN, Chehade R, et al. Analysis of rates of brain metastases and association with breast cancer subtypes in Ontario, Canada. *JAMA Netw Open*. 2022;5:e2225424.
8. Sperduto PW, Kased N, Roberge D, et al. The effect of tumor subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer. *J Neurooncol*. 2013;112:467-472.
9. Leone JP, Leone BA. Breast cancer brain metastases: the last frontier. *Exp Hematol Oncol*. 2015;4:33.
10. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372:724-734.
11. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367:1783-1791.
12. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: Exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial. *Ann Oncol*. 2020;31:1350-1358.

13. Sanglier T, Shim J, Lamarre N, et al. Trastuzumab emtansine vs lapatinib and capecitabine in HER2-positive metastatic breast cancer brain metastases: a real-world study. *Breast*. 2023;69:441-450.
14. Hurvitz SA, Modi S, Li W, et al. 377O A pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. *Ann Oncol* 2023;34:S335-S336.
15. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382:597-609.
16. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with Tucatinib Plus Trastuzumab and Capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38:2610-2619.
17. Hurvitz SA, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer patients with brain metastases from the randomized DESTINY-Breast03 trial. *ESMO Open*. 2024;9:102924.
18. Bartsch R, Berghoff AS, Furtner J, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. *Nat Med*. 2022;28:1840-1847.
19. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387:9-20.
20. Tsurutani J, Jacot W, Yamashita T, et al. 388P Subgroup analysis of patients (pts) with HER2-low metastatic breast cancer (mBC) with brain metastases (BMs) at baseline from DESTINY-Breast04, a randomized phase III study of trastuzumab deruxtecan (T-DXd) vs treatment of physician' s choice (TPC). *Ann Oncol* 2023;34:S342-S343.
21. Ma X, Long L, Moon S, et al. Comparison of population characteristics in real-world clinical oncology databases in the US: Flatiron Health, SEER, and NPCR. *medRxiv* https://doi.org/10.1101/2020.03.16.20037143:2020.03.16.200371432023, preprint: not peer reviewed.
22. Birnbaum B, Nussbaum N, Seidl-Rathkopf K, et al. Model-assisted cohort selection with bias analysis for generating large-scale cohorts from the EHR for oncology research. arXivLabs. 2020. Accessed May 19, 2024. https://arxiv.org/abs/2001.09765
23. Schettini F, Chic N, Brasó-Maristany F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer*. 2021;7:1.
24. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16:1141-1154.
25. Darlix A, Louvel G, Fraisse J, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. *Br J Cancer*. 2019;121:991-1000.
26. Epaillard N, Lusque A, Jacot W, et al. Incidence and outcome of brain and/or leptomeningeal metastases in HER2-low metastatic breast cancer in the French ESME cohort. *ESMO Open*. 2024;9:103447.,
27. Martin AM, Cagney DN, Catalano PJ, et al. Brain metastases in newly diagnosed breast cancer: a population-based study. *JAMA Oncol*. 2017;3:1069-1077.
28. Sun MS, Yun YY, Liu HJ, et al. Brain metastasis in de novo breast cancer: an updated population-level study from SEER database. *Asian J Surg*. 2022;45:2259-2267.
29. O'Sullivan CC, Ballman KV, McCall L, et al. Alliance A011801 (compassHER2 RD): postneoadjuvant T-DM1 + tucatinib/placebo in patients with residual HER2-positive invasive breast cancer. *Future Oncol*. 2021;17:4665-4676.

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